Analgesics

Opoid analgesics and antagonist

- Steps in Treating Pain :-
1) eleminate the cause of pain ex: having surgry for appendicitis
2) Take drugs such as analgesics either central or peripheral acting.
3) ~~Skin puture~~ acupuncture

Pain is :-

unpleasant sensation and emotional experience associated with potential tissue damage

Tow compenet :-

1) Sensory => means Somatic neurons.

2) emotional => means sychological.

There fore if we have 2 patient complaing of the same intense pain & and we gaved them drugs but The ~~Respe~~ respond was diferent.

The first respond => Relieve of pain

the second respond => No Releave of pain because the drug only affect the sensory compenent.

Types of Pain according to the type of receptors:-

1) Nociceptor pain ⇒ due to stimulation of pain receptors which called nociceptors which through the afferent nerve transmit the signals to the CNS.

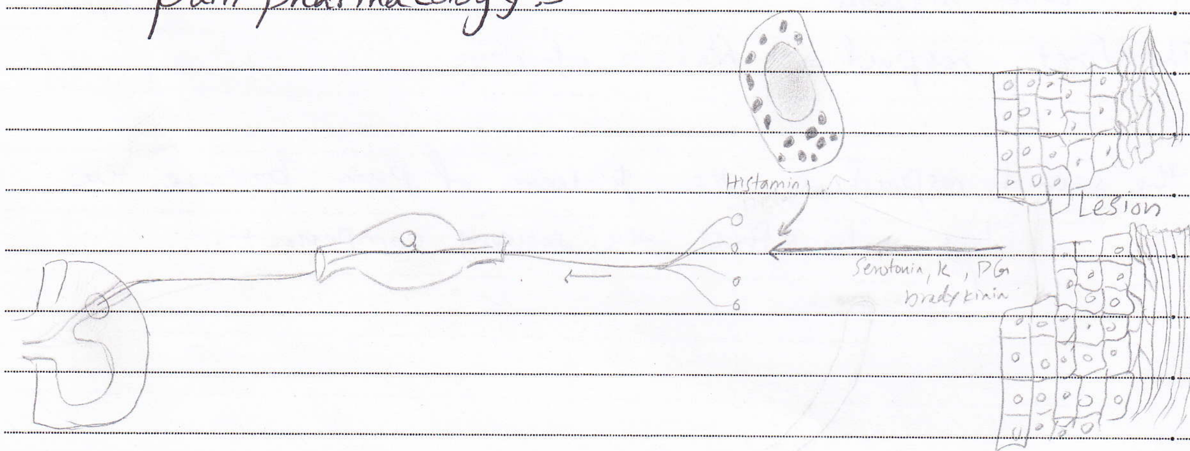
Nociceptor pain treated with opoid or NSAID.

2) Neurological pain ⇒ No activation of receptors. but due to damage of the neurons (CNS/PNS) "soma, axon" leading to diffuse neuropathy. change in connection & sensitivity

Treated with :-

1) antiepliptic drugs
2) anti depressant drugs
3) clonidine " α2 agonist "

Pain pharmacology :-



- Pain is mainly associated with tissue damage.
- Tissue damage means there is release of it's containt such as prostaglandins, K^+, serotonin, bradykinin acids. "All are called pain stimulus."
- They stimulate the ~~of~~ pain receptors "Nociceptors" which ~~increase the input~~ induce the stimulation of the first neuron
- also stimulate COX "cyclooxiginesen" which produce prostaglandin which increase the sensitivity ~~of~~ of the receptors.
- also activate Mast cells which release Histamine which Induce pain & signs of inflammation such as redness.

- In the spinal cord the first neuron release neurotransmitters that ~~the~~ activate the second neuron which lead to increase the input into the thalamus where pain perception occur.

- Then you feel pain which is Mild.

- if sever pain this ⟹ activate antinecicepthive pathway which release encaphalins, endorphines which interactive in the receptors of first neuron [μ, κ, δ]
activating these receptors leading to open K^+ channels & close Ca^{+2} channels ⇒ So decrease the release of neurotransmitters ⇒ Reduce the pain.

Morphine:

- MOA :-

① absorbed → act on morphine receptors → open K^+ ~~Ca^{+2}~~ channels & close Ca^{+2} channels → ↓ release of neurotransmitters. ⇒ * Inhibit pain perception.

② activate endorphine, encaphaline ⇒ * activate antinocicep[tive] pathway.

Analgesics :-

① opoid ⇒ act mailly on CNS "centrally acting".

② NSAID ⇒ act mailly by blocking Cox "prephrally acting".

Note :-

Asprin act central & prephral "90% Prephral"

Morphin act central & prephral "90% central"

So ingeneral opoid & NSAID have central & prephral action.

Opoids :-

- Drugs that releive pain, produce sedation without loss of conciousness.

- They are ⇒ natural « opium », semi-synthetic or synthetic

- Central acting, maily given post operative to relieve pa[in]

- used to called Narcotics but Not any More.
- Classification of opioids ⇒ I recomend to look for Page 2 in p.p.

Classification :-

1 Natural « opium alkaloid » :-
has More than 20 groups of drugs until now there is only two groups known.

@ phenanthrene

100 g opium has :-

analgesics:
- Morphine 10% "10g" ~~10gm~~
- Codeine 0.5% "0.5g"

- Thebaine 0.2%

- Morphine → More side effect such as Tolerance, dependence, Respiratory depression → can lead to arrest and death.
- Codiene ⇒ Mild analgesic & has less side effect + has anti tussive effect « anti cough »

So Now Morphine is changed into Codiene.

Structuraly Morphine has OH group while Codien has (CH_3O) metyle group. "Codien = ~~mytha~~ methyl-Morphine."
So in the body Codien is metabolised into Morphin & Produce dependence.

- So child taking Codien for cough may produce dependence. ↳ Linetascodien
- So it should be ~~used~~ used for 5 - 6 days to avoid the development of dependence.

ⓑ Benzylisoquinoline :- " Not analgesic "

- papaverine 1% ⇒ antispasmetic
  Like drugs which block muscarinic receptors M_2, M_3 on GIT so reduce spasm. ex :- - ATropin
  - - Bescupan
  - Propantiline

Note ⇒ papaverine use other mechanism, it dose not block muscarinic receptors.

Noscapine 6% ⇒ anti cough " dry cough "

[2] Semisynthetic :- Strong opoid

Change :-

Morphine → hydromorphone

Codiene → hydrocodon

Morphine → Diacethyl morphine " heroin "

- Morphine is Amphoter " 50% Lipid soluble, water ~~sol~~ soluble " So little amount pass through BBB. " limitted penetration ".
- Heroin. is Lipid ~~sol~~ soluble, 30 times stronger.

- Heroin is not used as analgesic due to its side effect
  but could be used in serious cases.

- Heroin is metabolized into Morphine.
- In the previous 2 group pt develop acute depence in the first dose then after 3-4 doses become depence.

[3] synthetic :-
are less dependence

1- Meperidine :-
- Rapid onset "immediat action"
  Short action. → Short Respiratory ~~system~~ depression
  less dependence.
  don't cause constipation.
  Toxicity ⇒ sizers, convulsions.

While Morphine :-
- long acting → long Respiratory depression
  if given during labour or ceserian may ~~case~~ cause Respiratory depression in fetus
- dependence, tolerance.
- constipation
- Toxicity ⇒ hypotention, agitation, fever, chills.

2- Methadone :-

- has withdrawal syndrome due to sychological and physical depence.

- Differe from Morphine in that this withdrawal syndrome is Mild, gradual of onset and slowly. " takes weeks "

- So it is used in treatment of addiction not intoxication.

  intoxication has to be treated immeditly.

- 100 mg ~~[illegible]~~ → (weeks later) 50 mg → (weeks later) 10 mg → (weeks later) Zero mg Placebo & pt not showing withdrawal syndrome

3- Fentanyl.

anasthetic, analgesic

produce sleeping, relieve pain

More active → used Transdermal to Relieve pain of MI, or other cordiac disease.

4- Tramadol

- less side effect

- ~~inhibit the release of serotonin~~

- inhibit the reuptake of serotonin leads to increase it's analgesic effect

- pt develope dependence. but less than morphine

pt ⇒ patient.

* opioid Receptors :- μ , k , δ , 6
  - are found in the brain , spinal cord , mesenteric plexus .
  - Block the release of neurotransmitters of any Neuron .

action of each receptors is in Page 3 .

- miosis means the drug is still in the plasma .
- two actions are Not tolerated ⇒ ① miosis
  ② Constipation
- Centrally → vagal stimulation $\xrightarrow{\text{Release Ach.}}$ Brady Cardia
- Peripherally → inhibit acetylcholin ∴ anticholinergic .

- # Drugs acting on μ are strong opioid .
  while those acting on k are moderate opioids

* Classification of opioid according to receptors :-
  Look page 3

- Antagonist ⇒ Drugs acting as for treatment of poisoning or intoxication with morphine . [Naloxone , Naltrexone]
  - Drugs acting as ~~treatment of addiction~~ .

- partial agonist are 90% of activity is agonist , 10% antagonist
  Should take care when used for releave of sever constant pain as it may cause withdrawal syndrome due to its 10% antagonist action .

- pentazocine is contraindicated in MI because it cause increase in cardiac activity "work" although it can be used for treatment of sever pain.

- if morphine is not available don't use pentazocine in MI instead use Buprenorphine.

- partial antagonist can be used for treatment of poisoning if Naloxone or Naltrexone are not available but take care of its agonist action as it can cause & worsen Respiratory depression.

* pharmacological action of opioid :-

It's action depend on the type of neuron

Types of neurons in the CNS are :-
① Excitatory neurons → release excitatory transmitters
② inhibitory neurons → " inhibitory transmitters

Ex:-
① Excitatory neurons releasing Aspartate that stimulate ACTH release
when Morphine act on opioid receptors "found on this neuron" it ~~cause~~ inhibit Aspartate

"Inhibition"

release so there is areduce in ACTH release.

② inhibitory neurons that release dopamine which control Prolactine release "inhibit its release".

"Stimulation" when Morphine act on ~~this~~ its receptor on inhibitory neurons it inhibit dopamine release so Increase Prolactine release

- By this we conclude that Morphine act by inhibition or stimulation.

[1] Central effect :-

- Analgesia "inhibition"
- Sedation, drowsiness
- euphoria "Stimulation"
- Respiratory depression "inhibition"
- Depression of cough reflex. "Inhibition"
- Nausea & vomiting "Stimulation of CTZ"
- miosis "inhibition of edenger nucleus of 3rd cranial nerve."
- Tolerance
- Dependence
- ↓ ACTH "Inhibition"
- ↑ prolactine. "Stimulation"
- in Posining → No need for emetic drugs as it cause vomiting.

Notes :-

- morphin can't be used as Anticough in the clinic but we can Use codine for short time to avoid dependence

- Contraindication of morphine is

① It cause increase ICP so not given in Head injuries but may given in pain of bone Fracture.

action :- it cause Respiratory depression → ↑ CO_2 Ins Brain → vasodilation → odema → Increase ICP.

② when looking for signs of deteroration which is Moisis and vomiting so the use of Morphine will make it defficult.

[2] CV effect :-

Morphine ⇒ Direct vasodilation of Both resistant and capacitant vessels

Means :-

it shift the blood from pulmonary circulation to systemic circulation

This is good for pt with pulmonary odema due to LVF

Morphine can't be used for pulmonary odema without Heart disease. "Here it is contraindicated"

- Conclusion :-

pt suffreing from sever pain and pal. odema of LHF

Because :-

Morphin can → vasodilation.

shife from pul. to systemic circulation.

releive ~~anxious~~ anxious.

[3] GI - effect :-

1- Constipation By ⇒ ↓ peristalsis → ↑ time of content stay in ~~stomach~~ GIT → ↑ water reabsorbtion

→ ↓ central attention for defecation reflex.

2- biliary tract spasm → constriction, spasm of sphincter of oddi.

→ ↑ intra biliary ~~colic~~ pressure ⇒ So ① Morphine can't be used ~~but~~ for ~~treating~~ biliary colic but can use Betteline ((Short action))

② or use anti-muscarinic drugs which block the receptor & prevent the spasm. then use morphine.

3 - Bronchospasm

4 - urinary retention → contraction of urinary sphincter.

5 - ~~urinary~~ uterine spasm.

تنويه :- morphine is used in sever constant pain not intermitten pain. The last can be treated with aspirine.

- In Sever Pain due to acute abdomine or burn Morphine can not be given.

Acute abdomine :-
first diagnoss should be done before Morphine add ministrator. which can relieve the pain while perforation occure but masked by Aspirine ?

Burn :-
- lead to toxitcy if morphine is used.
- due to constriction of the physiological volume "loss of Plasma"
- first correct the Plasma volume
- In this case when you give the first dose you add another one ~~ba~~ ~~to~~ So become concentrated in the plasma

Phamacokinatics :-
- absorption from skin, GI tracte, lung subcutaneous, intramuscular, intravenous route.

- Morphine Metabolize into active metabolite "analgesic" "morphine 6-glucuronide"

- Pethidin is metabolised into Nor-meperidine which produce excitatory seizure

Therapeutic uses :-

look page 6

- Sever pain of cancer for example. terminal illness
- MI " vasodilation, ↓ Cardiac work
- internal bleeding } ?

Note page 5,6 is very important to read

* Antitussive Drugs :- Look page 6

Codiene, dextromethorphan, ~~levo propoxy~~ levo - propoxyphene.

when you combine reduce the dose.

~~etc~~

* Drug for neurological pain :-

Tricyclic antidepressant like amitriptyline

Look page 6

* Antiepileptic drugs :

carbamazepine, phenytoin, gabapentin, clonidine.

* Drug interaction :-

- Alcohol or barbiturate for example exhibit ~~it~~ intense ~~effects~~ sedative effect.
- ↑ sedation and toxicity when combined with diazepam.

Written By :- Liza Ali Obaid. wish you all the best.